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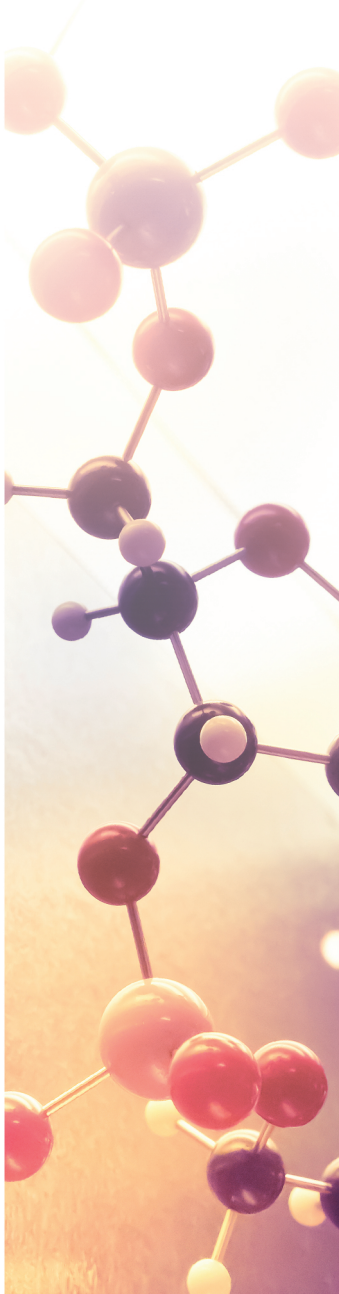

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REVIEW

EXTEMPORANEOUS COMPOUNDING FOR CHILDREN WITH HEART DISEASE IN JAMAICA

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ABSTRACT

Background: Congenital heart disease (CHD) has an incidence of approximately 8 per 1,000 live births globally. Treatment of heart disease in the pediatric population is largely dependent on the underlying cause and the child's age. Drug therapy is commonly employed for managing children with cardiac failure and other heart related conditions. Overall, few drugs are approved for use in pediatric patients, guided by evidence-based tri-als conducted in adult population. Studies in Europe, North America and Canada indicate that about 80% of prescriptions for managing pediatric heart conditions are used as unlicensed or as off-label products. Such studies in the Caribbean populations are lacking in the literature. This study was therefore designed to investigate the methods by which children with heart failure are being managed in Jamaica, West Indies.

Method: A real-time prescription screening and retrospective survey of compounding record of medications compounded and dispensed for children age 0 to 12 years was done during a period of 12 months at the Bustamante Hospital for Children, Jamaica. A validate data sheet was used to collect demographic (child's age, gender), diagnostic and pharmacotherapeutics data on patients after securing informed consents from their parents. In addition, historical data were extracted from an onsite compounding logbook. Pharmacotherapeutics information include drug prescribed, dose size and dosing frequency, dosage form and its age-appropriateness of medication prescribed. For lack of age-appropriate medications, compounding or modification performed, volume compounded and dispensed extracted. Data were analyzed using SPSS Version 19 and MS Excel.

Results: a total of 3,747 prescriptions were surveyed with 10,797 items prescribed. Of the items prescribed heart specific medicines represented 5.23% (565). The mean age of children was 62.55 months (SD = 31.02) with 53.33% of them being male patients. Among the top twenty drugs prescribed for children, only three (3) were for cardiovascular indication i.e. captopril (1.33%), furosemide (3.49%) and spironolactone (3.35%). Approximately 76.11% of these prescriptions was either compounded or manipulated to provide child-appropriate dosage forms.

Conclusion: Extemporaneous compounding is still being used to provide age-appropriate dosage forms for pediatric patients with heart disease in Jamaica. Therefore, there is ongoing need for validation of compounding practices with regard to the quality of the practice and the quality of the finished preparations.

Children Hospital Pharmacy – Compounding – Pediatric Heart Disease

RESUMEN

Introducción: A nivel mundial, la cardiopatía pediátrica (CHD) tiene una incidencia de aproximadamente 8 de cada 1.000 nacimientos . El tratamiento de la CHD pediátrica depende en gran medida de la causa subyacente y la edad del niño. Los niños con insuficiencia cardíaca y otras afecciones relacionadas con el corazón son tratados con fármacos.

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En general, pocos medicamentos están autorizados para su uso en pacientes pediátricos, guiados por evidencias basadas en ensayos clínicos realizados en la población adulta. Los estudios realizados en Europa, América del Norte y Canadá indican que alrededor de un 80% de las prescripciones para el tratamiento de cardiopatías pediátricas se utilizan como productos off-label o no autorizados. Tales estudios escasean en las poblaciones caribeñas.

Por lo tanto, este estudio fue diseñado para investigar los métodos por cuales los niños con insuficiencia cardíaca se están tratando en Jamaica.

Método: Se realizó una revisión en tiempo real de las prescripciones y una encuesta retrospectiva del registro de compuestos de los fármacos preparados y dispensados para niños de 0 a 12 años durante un período de 12 meses. Se utilizó una hoja de validación de datos para recopilar datos demográficos (edad del niño, género), de diagnóstico y farmacoterapéuticos en pacientes después de obtener el consentimiento informado de sus padres. Además, se obtuvieron datos históricos de un libro de registro de compuestos. La información farmacoterapéutica incluye el medicamento prescrito, dosificación y frecuencia, forma de dosificación y adecuación del medicamento prescrito en función de la edad. Por falta de medicamentos apropiados para la edad, preparados o modificaciones realizadas, volumen compuesto y dispensado extraído. Los datos se analizaron utilizando SPSS Versión 19 y MS Excel.

Resultado: Se revisaron un total de 3.747 prescripciones con 10.797 ítems prescritos. De los ítems prescritos, los medicamentos específicos para el corazón representaron el 5,23% (565). La edad media de los niños fue de 62,55 meses (SD = 31,02), siendo el 53,33% de ellos pacientes varones. Entre los veinte principales medicamentos recetados para niños, solo tres (3) fueron para indicación cardiovascular, es decir, captopril (1,33%), furosemida (3,49%) y espironolactona (3,35%). Aproximadamente el 76,11% de estas prescripciones se elaboraron o utilizaron para proporcionar formas de dosificación apropiadas para niños.

Conclusión: La preparación extemporánea se utiliza en Jamaica para proporcionar formas de dosificación apropiadas para la edad de los pacientes pediátricos con cardiopatías. Por lo tanto, hay una necesidad constante para la validación de las prácticas de elaboración con respecto a la calidad de la práctica y la calidad de las preparados terminados.

Farmacia hospitalaria para niños– Preparados – Cardiopatía pediátrica

INTRODUCTION

Heart disease (HD) implies various conditions that affect the heart and its normal function.[1] In the pediatric population, HD may be congenital —arising from a birth defect or acquired.[2, 3] Acquired heart disease (AHD) may be present in children with structurally normal heart and are usually due to cardiac and non-cardiac causes.[5, 6] Rheumatic heart disease (RHD) is an example of AHD which is responsible for 20.1% of HF in children while congenital cardiomyopathies accounted for an estimated 16.8% of HF in children. RHD is said to cause 233,000 to 492,000 deaths each year with an estimated 95% occurring in developed countries.[7] Children diagnosed with HD may experience motor, physical or cognitive impairment and overall, poor quality of life.[4]

Heart failure (HF) is a known complication of HD, and is defined as a clinical syndrome characterized by the inability of the heart to maintain cardiac output at a pace necessary to meet the metabolic demands of the body.[9] In addition, patients that have undergone surgical repairs may sometimes experience residual damage to the heart. HF in children usually results from a clinical syndrome presented as circulatory disturbances due to volume overload (usually seen in large ventricular septal defect) or obstruction to flow (commonly observed in aortic stenosis). In developing countries, structural heart defects are the leading cause of HF in infants and children.[3, 6, 8] Due to the varied etiologies of HF in children, diagnosis is usually a challenge, and can have different clinical presentations among children of different age groups.[8]

The New York Heart Association (NYHA) Heart Failure Classification established in 1987 is more appropriate for assessing adults' HF than children, especially infants. The Ross Heart Failure Classification was therefore developed as a more appropriate instrument for children.[10, 11] The instrument utilizes parameters such as feeding difficulties, growth problems, and symptoms of exercise intolerance. In addition, there is the New York University Pediatric Heart Failure Index based on a scoring systems ranging from 0 (no heart failure) to 30 (severe heart failure) for classifying HF in the pediatric population.[10] The American College of Cardiology and the European Society of Cardiology also have established guidelines to aid in the management of patients with CHD and HF.[12-14]

The incidence of HF in children is poorly established. However, causal factors such as CHD has an incidence of approximately 8 per 1,000 live births of which, due to early surgical intervention, only 1 to 2 per 1,000 live births may develop HF annually. In the UK, approximately 0.87 per 100,000 upon first assessment on hospitalization are diagnosed with HF. In Nigeria, 7.02% of all emergency admissions to tertiary hospitals are diagnosed with HF.[15]

Treatment of HF in children is largely determined by the underlying cause and the child's age. The standard approach is to correct the underlying cause, minimize morbidity and mortality and, improve functional status and quality of life.[10] Generally, management is aimed at maximizing cardiac output and tissue perfusion while reducing stress responsible for increase in myocardial oxygen consumption (MVO_2).[6] Providing nutritional support is fundamental in managing children with HF since they usually present with growth retardation resulting from low caloric intake.

Drug therapy is commonly employed for managing children with cardiac failure and other heart related conditions.[14] Overall, few drugs are approved for use in pediatric patients resulting in the unlicensed or off-label drug usage.[16, 17] The uses of such drugs are guided by evidence-based trials conducted in the adult population. The general approach to pharmacotherapeutic management of HF in pediatric population is to employ a combination of clinical experiences, small scale studies in the pediatric population and the application of data obtained from adult cardiology.[9, 14]

The lack of appropriate drug products for pediatric patients and special populations often necessitate extemporaneous compounding in which pharmacists prepare «in house» formulations following established United States Pharmacopeia (USP) guidelines.[18] The specific requirements of medicines for children vary within the pediatric age group, and are influenced by factors such as: the inability to swallow solid dosage forms (tablets and capsules), unacceptable taste of certain medicines, need for specific dosing concentration and frequency.

Drugs with no available liquid formulation available are often manipulated or modified by the pharmacist to provide age- or medical condition-appropriate formulations for children.[19, 20] Tablets and capsules are commonly used to prepare oral liquids while scored tablets may be split to make them more convenient for administration to children.[21] Overall, the consideration to compound and choice of appropriate compounding method requires the ascertainment of non-availability of commercial products approved for children as well as considerations for risk of aspiration or choking with solid dosage forms alternatives, dosing volume and tolerance for specific excipients.[22, 23]

Rationale. A plethora of information is available on compounding and the use of medicines in an off-label and unlicensed manner in regions such as North and South America, Australia and the Middle East. The range of data available in the literature covers age 1 day to 18 years.[24] For example, Dutch hospital pharmacies provide «in house» pediatric formulations or modify commercial preparations such as capsules to provide age-appropriate suspensions.[25] Similarly, in the Netherlands, processes such as tablet and suppository splitting, as well as capsules emptying to prepared suspensions, have been reported.[20] On the other hand, special manufacturing licenses are issued for the preparation of medicines under the good manufacturing practices in the UK. However, in all these approaches, formulations are not formally tested in clinical trials in pediatric populations.[5, 26, 28] Information about how pediatric patients with heart diseases are medicated in Jamaica is lacking in the literature, which justifies the need for the present study.

Objectives. Anecdotal evidence suggests that there is an increase in population of children presenting with heart disease in Jamaica and the extent of availability of proprietary medications for managing these conditions was uncertain. In line with literature information on how this situation is being managed in other countries,[5, 16, 26] we hypothesized that off-label prescribing and extemporaneous compounding were being used to satisfy pediatric need in Jamaica. The objectives of this study were to:

a. Determine the extent of magistral compounding in Jamaica through a survey of prescribing and compounding practices occurring at the Bustamante Hospital for Children (BHC), a major pediatric hospital in Jamaica.
b. Identify the drugs that are being used to manage pediatric heart conditions.
c. Analyze the types of compounding, manipulation or modification techniques that are being used to provide age-appropriate medicines for children from commercial drug products or bulk drug substance.

METHOD

Design. A cross-sectional retrospective survey of children age 0 to 12 years was conducted at the BHC outpatient pharmacy department for a period of 12 months. Eligibility criteria for patients' record selection were: prescription was for a child (age 0 to 12 years); the child presented with heart disease; commercial product was not available for managing the condition in an acceptable form for the child and, hence, compounding of modification to an existing drug product has to be done to satisfy the child's need. Data was extracted from selected prescriptions that were received and processed at the pharmacy department for patients that met previously stated eligibility criteria. Using the same protocol for case selection, additional information on compounding was gathered from an onsite-compounding logbook. A representative sample of prescriptions to be surveyed was selected using the randomization function in Microsoft Office Excel spreadsheet and the quantity of prescriptions to be surveyed was calculated using Eq. 1:[28]

$$n = \frac{Z^2 P (1 - P)}{d^2}$$

TABLE 1. The twenty (20) annual most frequently prescribed drugs for oral administration at the BHC outpatient pharmacy department.

Drug	*Prescription frequency*	*% Prescribed*
Amoxicillin	662	11.61
Amoxicillin & clavulanic acid	840	14.73
Beclomethasone	101	1.77
Captopril	76	1.33
Cefuroxime	167	2.93
Co-trimoxazole	142	2.49
Diclofenac potassium	480	8.42
Diphenhydramine	211	3.70
Erythromycin	161	2.82
Furosemide	199	3.49
Griseofulvin	60	1.05
Ketoconazole	84	1.47
Loratadine	95	1.67
Mebendazole	63	1.11
Metronidazole	90	1.58
Paracetamol (acetaminophen)	998	17.51
Prednisolone	307	5.39
Salbutamol (albuterol)	774	13.58
Spironolactone	191	3.35
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Note: Drugs in the form of semi-solids (ointments, creams, pastes and gels), sprays and drops were grouped into a category labeled as «Miscellaneous».

Where n is the sample size, Z is the Z statistic for a 95% level of confidence (1.96), P is the expected prevalence in compounding (0.5 or 50) and d represents precision (0.02 or 2%). The minimum prescriptions to be surveyed were found to be 2,401. Approximately 35,971 prescriptions were processed annually at the BHC outpatient pharmacy department with a monthly average of 2,997 (SD = 266). However, at the end of the randomization of the months and weeks to be sampled, a total of 3,747 prescriptions were surveyed with 10,797 items being prescribed of which 5,277 (48.9%) were manipulated before dispensing to pediatric patients. To guide the data collection process, the method of data collection, the source of data (prescriptions) and coding and data entry into computer the process was pre-tested for one month.

The variables documented from each prescription were age, gender, drug name and drug class, dose size, dose frequency, type of dosage form prescribed and its suitability for children, compounding/modification performed and type and volume compounded and dispensed. Generally, in this study, solid dosage forms (tablets and capsules) were categorized as inappropriate for children less than six years while any product not specifically recommended for children under 12 years were categorized as unlicensed drug use for children.

Pediatric patient age classification. For the purpose of the study, prescriptions were categorized into Neonate (Less than one month, or 0 to 28 days), Infants (one month or older than 28 days to 12 months), Children (above 12 months to 144 months), Other (above 144 months) and Unknown (prescriptions with no age information recorded) following the guidelines of the American Academy of Pediatric Committee on Fetus and Newborns, and the International Conference on Harmonization.[30-32]

All drugs prescribed were documented and their pharmacological class identified. The suitability or appropriateness of the drugs was also documented based on two parameters: the age of the patient, and the type of dosage form prescribed and dispensed. For the purpose of the study, drugs that were available as solid dosage forms (tablets and capsules) were considered inappropriate for children below 12 years of age. All administered drug products were identified as compounded or not compounded and information on compounding was extracted from each prescription. Furthermore, compounded drugs category was classified according to the forms of manipulations such as powder or granule for reconstitution, tablet splitting, tablet crushing, capsule emptying, and other (semisolid compounding etc.).

Data analysis. Data were analyzed with Statistical Package for Social Sciences (SPSS software) Version 19. Microsoft Office Excel was also used to aid in presentation of results. Pairwise comparisons were made using student t-test while multi-factor comparisons and test of significance were done with Analysis of Variance (ANOVA). The proportion of the parameters documented was determined and all differences tested for statistical significance at 5% level of variation (p-value = 0.05, equivalent to 95% confidence level).

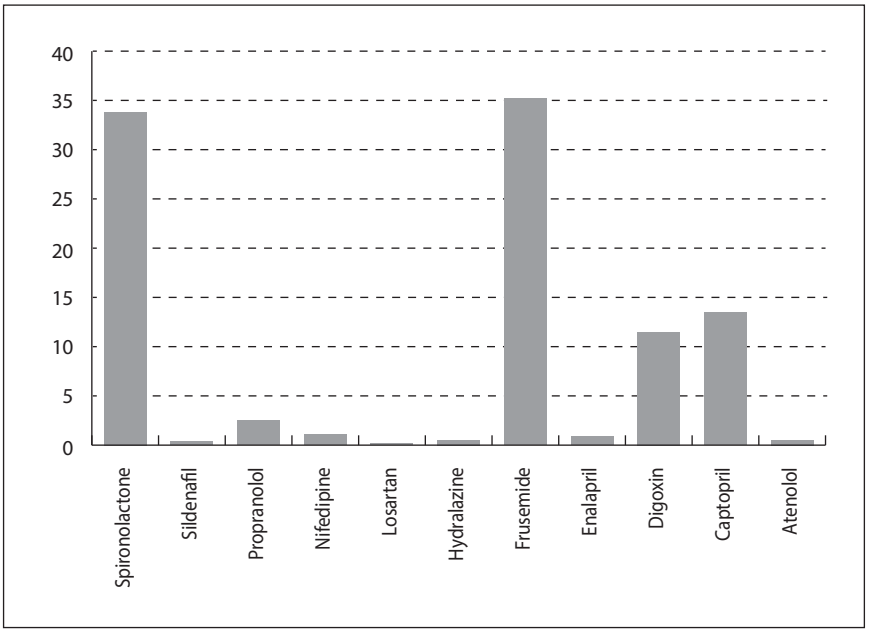

FIG. 1. Percent annual prescription and dispensing of pediatric cardiovascular drugs at the BHC out-patient pharmacy department.

RESULTS AND DISCUSSION

Incidence of prescription for pediatric patients. This study was designed to examine drugs prescribed for children with heart disease —more specifically heart failure— and which require reformulation to provide age-appropriate medicines. Overall, of the 10,797 drugs prescribed, 5.23% (565) were cardiovascular-specific. The drug classes include those on the World Health Organization (WHO) Essential Medicines list (EML), namely beta-blockers, angiotensin converting enzyme inhibitors (ACEI), diuretic (loop and potassium sparing), and inotropic agents. Captopril (1.33%), furosemide (3.49%) and spironolactone (3.35%) were among the top twenty prescribed drugs (Table 1).

Among the top twenty drugs prescribed are shown in Table 1. Cardiovascular drugs by therapeutic category are shown in Fig. 1. The proportion compounded ranged from sildenafil (3%) to digoxin (16%). Of the 10,797 annual prescriptions, 565 representing 5.14% of prescriptions contained heart-specific cardiovascular drugs. Approximately 80% of prescriptions for children at the BHC are used as unlicensed or off-label prescriptions, consistent with reports in the literature.[17, 19, 20] The US Food and Drug Administration (FDA) define «off-label» drug use as «unapproved use of a licensed drug» or as a use «outside the term of the licensed label». The therapeutic categories of cardiovascular drugs commonly compounded at the BHC are shown in Fig. 2. The licensed label refers to the official drug description of a drug product, giving detail information on indication, who should take it, adverse effects, instruction for use, and safety information.[23] Due to lack of licensed drugs for pediatric population, modification of a licensed medicine or «specials» medicine, use of chemicals as medicine, and the use of medicine before a license is granted referred to as «unlicensed» drug use is common practice.[29] To address the shortage of licensed drug products for children, the FDA issued the pediatric exclusivity under the FDA Modernization Act (FDAMA).[30] The aim of this initiative was to encourage research and development of drug products for children. Implementation of the FDAMA in 1997 was followed by the Best Pharmaceuticals for Children Act (2002) and the Pediatric Rule.[33] Patent extension of drugs with pediatric labeling is also facilitated under these initiatives which further encouraged the development of safe and effective drug products for children.[34]

In December 2007, WHO launched the Better Medicines for Children (BMC) initiative.[36] Data from Europe showed that only 35% of drugs used in children were approved for such use. There is an overwhelming need for the availability and access to «child friendly» formulations, research, and the use of medicines in an efficient and appropriate manner. Under the general framework of making medicines more suitable for children, the Essential Medicine List (EMLc) was prepared together with children formulary and child friendly formulations. The process involved health policy decision makers, health care professionals, and other representatives of people involved in BMC research on children. However, the financial reward and recovery of investments from extensive and elaborate studies involving children is not encouraged by the relatively small market.[37, 38] Other limitations include the need for ethical clearance for conducting research in children, problems with blood sampling, difficulty recruiting children and lack of funding.[25, 26, 39] Thus, despite the significant impacts of various initiatives to make medicine available for children population, there is still a number of limitations that would make extempora-

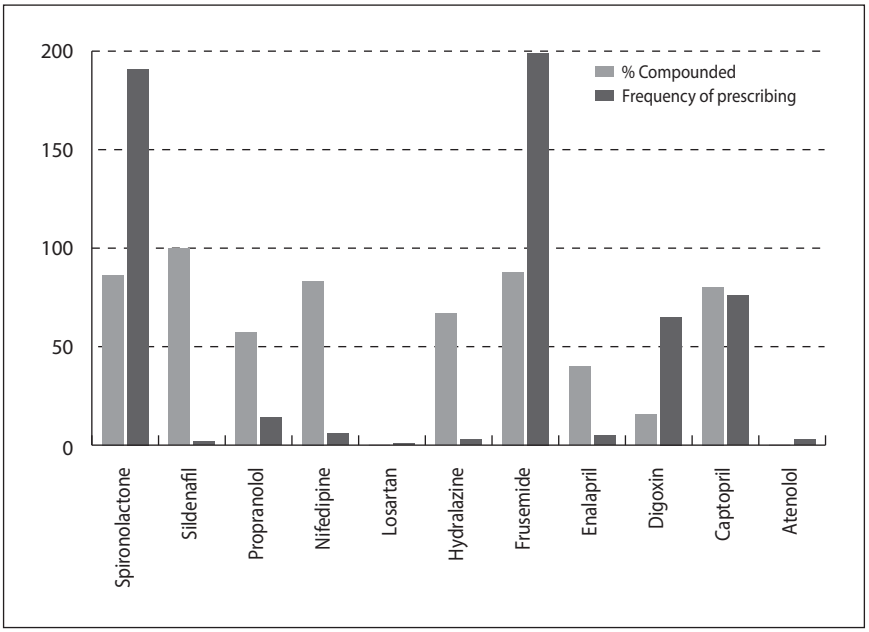

FIG. 2. Cardiovascular drugs pediatric prescription frequency and % of prescriptions of each drug that were compounded annually at the BHC out-patient pharmacy department.

neous compounding relevant in satisfying pharmacotherapeutics need of pediatric population.

Pediatric Patient characteristics. The findings shows that the mean age documented on each prescription was 62.55 months (SD = 31.02). Overall, the children age category accounted for most of the prescriptions dispensed 2,838 (75.74%) while neonates, infants, and adolescents were 38 (1.01%), 780 (20.82%) and 19 (0.51%) respectively; only 72 (1.92%) prescriptions lacked age information (Fig. 3). According to Nousi and Christou (2010),[40] CHD are the leading cause of death in infancy and childhood especially in the developing countries. Heart diseases affect more than 600,000 children in the United States.[41] Overall, approximately 60% of the 25 thousand infants born with the disease reach adulthood.

A total of 1,961 (53.33%) and 1,699 (45.34%) prescriptions were written for male and female patients respectively; a small proportion (87 or 2.32%) were not gender-classified. 266 (or 47.84%) of male and 223 (or 40.11%) of female were administered drugs for managing cardiovascular conditions while 64 (or 12.05%) were unknown. Studies of a northern Iranian neonate population between 2007 and 2008 indicated that heart diseases were more common in male births.[3] However, studies in other regions of the world showed conflicting reports. Findings in Saudi Arabia and Iceland indicated similarity in incidence of CHD among genders while the incidence was greater among female neonates of Nigerian population.[3] In Jamaica, the average annual age distribution of children receiving medicines for managing heart failure were two neonates (0.36%), 199 infants (36.05%), 340 children (61.59%), and 11 unclassified (2%) of a total pediatric population of 556 (Fig. 3).

Prescribing pattern for pediatric patients. A summary of the most frequently prescribed oral dosage forms is shown in Table 1 (No. = 5,701). The most commonly prescribed drugs included: paracetamol (17.51%), amoxicillin-clavulanic acid (14.73%), salbutamol (13.58%), amoxicillin (11.61%) and diclofenac potassium (8.42%). Of all drugs prescribed, 565 (5.14% of 10,797) were for patients with cardiovascular diseases. Commonly prescribed pharmacotherapeutics classes include angiotensin converting enzyme inhibitor (ACEI), beta-blocker, cardiac glycosides, diuretics (loop and potassium sparing) and aldosterone antagonist, calcium channel blocker, peripheral vasodilator and selective inhibitor of cyclic guanosine (Fig. 1). Of the 565 prescriptions, furosemide accounted for 199 (35.22%), spironolactone 191 (33.81%), captopril 76 (13.45%), digoxin 65 (11.5%) and propranolol 14 (2.48%) (Fig. 1). About 430 (76.11%) of the doses were manipulated or compounded while 135 (23.89%) were dispensed in their original dosage forms. Sildenafil (16%), furosemide (14%), nifedipine (14%), spironolactone (14%), and captopril (13%) top the list of drugs compounded before dispensing to children (Fig. 2). Other drugs that were compounded to lesser extent include hydralazine (11%), propranolol (9%), enalapril (6%) and digoxin (3%). The drug classes prescribed by age and gender are shown in Fig. 3.

Literature indicates that over half of the pharmacological interventions used for hospitalized children are off-label or unlicensed drugs due to lack of licensed products and the wide range of dosage amount for the different age groups (neonates to adolescents).[5, 27] The manipulation or alteration of licensed medicinal products is a common practice when individualizing drug therapy for this population. However, the safety and efficacy profiles of medications may be significantly different for children than

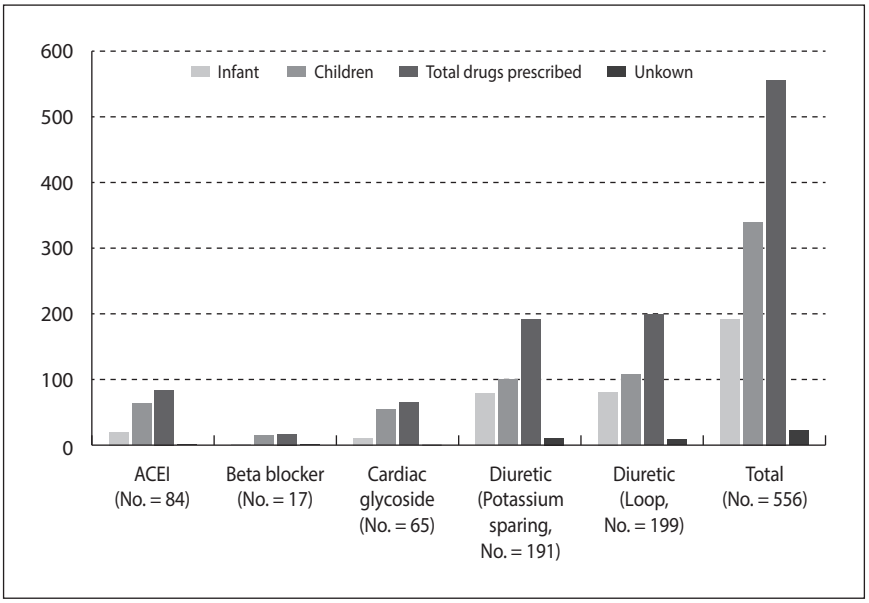

FIG. 3. Heart-specific cardiovascular drugs prescribed and dispensed at the BHC out-patient department by age classification during a 12-month period.

adults due to differences in developmental physiology, disease pathophysiology, or developmental pharmacokinetics and pharmacodynamics.[42, 43]

Lack of patient-friendly dosage forms naturally results in the use of unlicensed drug products. The four main patterns of unlicensed drug use are: (1) extemporaneous compounding, (2) manipulation of products by caregivers, parents or patients, (3) use of imported drugs approved in other countries, and lastly, (4) the use of «specials» medicines manufactured under a license by regulatory authorities.[44] A high level of compounding was observed (76.11%; No. = 565) for cardiovascular drugs that were prescribed. Drug products containing captopril, furosemide, nifedipine and spironolactone had greater than 80% of the prescribed doses manipulated (Fig. 2). This is much higher than the levels of compounding found in other countries.[5, 24, 44, 45]

Overall, a low incidence of extemporaneous compounding for pediatric patients with heart condition was observed in this study. The challenges of using an unlicensed or off-label drug for children through extemporaneous compounding revolve around safety and stability. Incidence of adverse drug reactions, poor product quality and stability have been reported.[23, 46] It is therefore known that, following manipulation of drug products, safety and stability of compounded medicines may not be guaranteed. In addition, post-processing storage and transportation may further complicate the safety, efficacy and stability of the products. Generally, compounded aqueous liquid medicines are assigned a standard beyond use date (BUD) of 14 days if patients follow the recommendation to refrigerate the products.[45, 47, 48] As additional measures, most compounding facilities keep their formulations very basic and exclude preservatives and suspending agents [49] to minimize unpredictable interactions or adverse effects. In addition, liquid preparations are generally compounded with proprietary tablets or capsules as the source of the active ingredient, 20% syrup as sweetener and defined color for product identification.

CONCLUSION

The study showed that unlicensed or off-label drug products were being used for managing pediatric population at the BCH in Kingston, Jamaica. Lack of drug products specifically licensed for children and the need to provide customized drug therapy are some of the main reasons why extemporaneously compounded medicines are being used for children with heart conditions. Extemporaneous compounding thus remains a key pharmaceutical care skill of pharmacists at the hospital. The findings of the study are consistent with literature information from other countries around the world. With the practice of compounding still relevant today, the quality assurance of such formulations is highly recommended, and where possible a standardized mechanism for utilizing extemporaneous compounded formulation(s) should be established by institutions. Quality assurance of compounding operations as well as finished product testing for chemical, physical and microbial qualities would significantly enhance the safety, efficacy and stability of compounded medicines. In addition, patients should be monitored for evidence of adverse drug reactions and for effectiveness of compounded drug therapy. Children with heart diseases are more likely to be non-adherent to drug therapy due to the presence of feeding and self-care challenges. This may also be complicated by increased pressure on the family both financially and psychologically. The lack of licensed marketed products, the need for compounded medicines and short beyond use dates of compounded medicines may add to the challenges these patients and

their families' experience. This study therefore supports the ongoing initiatives for provision of age-appropriate medicines for children and the need for rigorous quality assurance programs in compounding pharmacies to enhance the responsible and safe provision of drug therapy for the pediatric population. CP

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